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Review

Cardiac damage and tropism of severe acute respiratory syndrome coronavirus 2

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Until now, the World Health Organization registered over 771 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection worldwide, of which 6.97 million resulted in death. Virus-related cardiovascular events and pre-existing heart problems have been identified as major contributing factors to global infection-related morbidity and mortality, emphasizing the necessity for risk assessment and future prevention.

In this review, we highlight cardiac manifestations that might arise from an infection with SARS-CoV-2 and provide an overview of known comorbidities that worsen the outcome. Additionally, we aim to summarize the therapeutic strategies proposed to reverse virus-associated myocardial damage, which will be further highlighted in this review, with an outlook to successful recovery and prevention.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by an outbreak of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has resulted in a global hampering and burden on health care systems. Infection with SARS-CoV-2 can range from asymptomatic to fatal, making it unpredictable. Fortunately, the majority of cases are mild infections, characterized by symptoms, such as fever, coughing, muscle pain, loss of taste and/or smell, headache, dyspnea, and fatigue, and do not typically require special medical attention [1]. However, severe cases have put a strain on intensive care units (ICUs) during the initial waves of the pandemic, often requiring mechanical ventilation and incurring high material and medication costs [2]. In-hospital mortality rates have significantly increased among ICU patients, with common causes of death, including septic shock, multiorgan failure, suppurative pulmonary infection, right ventricular congestive heart failure, and respiratory failure [3,4]. Pre-existing cardiovascular complications, such as hypertension, have been shown to contribute to worse outcomes, highlighting the importance of considering cardiac involvement during SARS-CoV-2 infections. Therefore, this review aims to summarize cardiac manifestations following infection, known comorbidities, and therapeutic approaches for intervention and prevention.

Cardiac infiltration by severe acute respiratory syndrome coronavirus type 2: molecular features and outcomes in hospitalized patients

Innate immune and inflammatory response

The pathophysiology of critically ill patients and autopsies in individuals who died from COVID-19 have been intensively investigated over the last years, leading to the identification of typical hallmarks of cardiac damage; these arise from dysregulated immune response [5], inflammatory bursts, often referred to as 'cytokine storms' [6], and pre-existing comorbidities [7].

The angiotensin-converting enzyme 2 (ACE2) receptor is widely known to be the primary contributor to cardiac SARS-CoV-2 infiltration. It internalizes ACE2 through the mediator transmembrane serine protease 2. Additionally, surface receptors neuropilin-1 and CD147 also promote viral

entry. Further evidence has shown that integrin α5β1 facilitates viral binding to ACE, Cathepsin B/L activates the viral spike protein through endosomal cysteine proteases, and extracellular vesicles are involved in cardiac infection [8]. Activation of the innate immune response is the first defense against viral uptake, leading to the recruitment and migration of immune cells into cardiomyocytes. However, SARS-CoV-2 can elude detection by the innate immune system and disrupt its signaling pathways. This is achieved through the biosynthesis of various viral proteins, which downregulate the expression of the key immune components, including interferon (IFN)-I and IFN-III, along with IFN-stimulated genes [9]. The delay of the IFN response engenders an insufficiency in the innate immune response, thereby facilitating viral persistence and prolonged tissue damage. Consequently, it triggers the sustained recruitment and release of myeloid cells, such as neutrophils and monocytes, to the infected site (Figure 1) [10]. Compared with SARS-CoV-2 polymerase chain reaction–negative postmortem tissue, recent findings in SARS-CoV-2-positive cardiac autopsies have shown significantly altered levels of various markers. These markers include CD42 (platelets), CD15 (myeloid cells), CD68 (macrophages and monocytes), C4d (complement component), fibrin (blood clot formation), and myeloperoxidase, which is a marker for neutrophil and neutrophil extracellular trap activation [11]. Another study conducted on heart autopsies from SARS-CoV-2 patients revealed a significant increase of perivascular CD11b/TIE2+ macrophages, which are responsible for intussusceptive angiogenesis. This phenomenon was not observed in autopsies of viral myocarditis (non-SARS-CoV-2) or in noninfected controls. These findings suggest a unique infection pattern with perivascular infiltration [12]. In addition, the group of Vannella et al. detected hyperdominant T cells directed toward SARS-CoV-2 in the myocardium, providing evidence for the involvement of T cells in the development of myocarditis and cardiac dysfunction [13]. The activity of immune cells is accompanied by a significant increase in inflammatory cytokines in the cardiac tissue and circulation of severely infected patients compared with noninfected controls [14,15]. Although the serum cytokine levels of mildly infected subjects were similar to those of the noninfected group, tumor necrosis factor-α (TNF-α) and CC-chemokine ligand 5 exhibited expression patterns comparable to those of severely infected patients [14]. The group of He et al. investigated the incidence of virus-induced myocardial injury in the enrolled patients. They observed this injury in 30.8% of the patients. Along with the injury, they found significantly elevated levels of inflammatory markers IL-1β, IL-6, IL-10, and TNF-α. TNF-α is an important early activator of proinflammatory signaling and immune cell infiltration [16]. These findings persisted in autopsies of patients who succumbed to the virus (32% in the injury group vs 2.5% in the noninjury group), indicating an ongoing hyperinflammatory state [17]. Notably, the work of Karki et al. concluded that the interplay between TNF-α and IFN-γ plays a pivotal role in conveying inflammation-induced cell apoptosis [18].

Multiple publications have focused on examining the genomic changes related to an infection with SARS-CoV-2. One study found 86 genes and 15 microRNAs to be differentially regulated in infected human cardiomyocytes, targeting proteins involved in the inflammatory response [19]. These findings were further strengthened by the GenOMICC study, which conducted whole-genome sequencing in 7491 severely infected patients. The study found significant alterations in genes involved in the interferon signaling, leucocyte differentiation, and blood-type antigen secretor status, identifying potential targets for intervention [20]. Massive analysis of cDNA ends–RNA sequencing further revealed expression alterations associated with immune response and cardiomyocyte damage linked to virus infiltration [21].

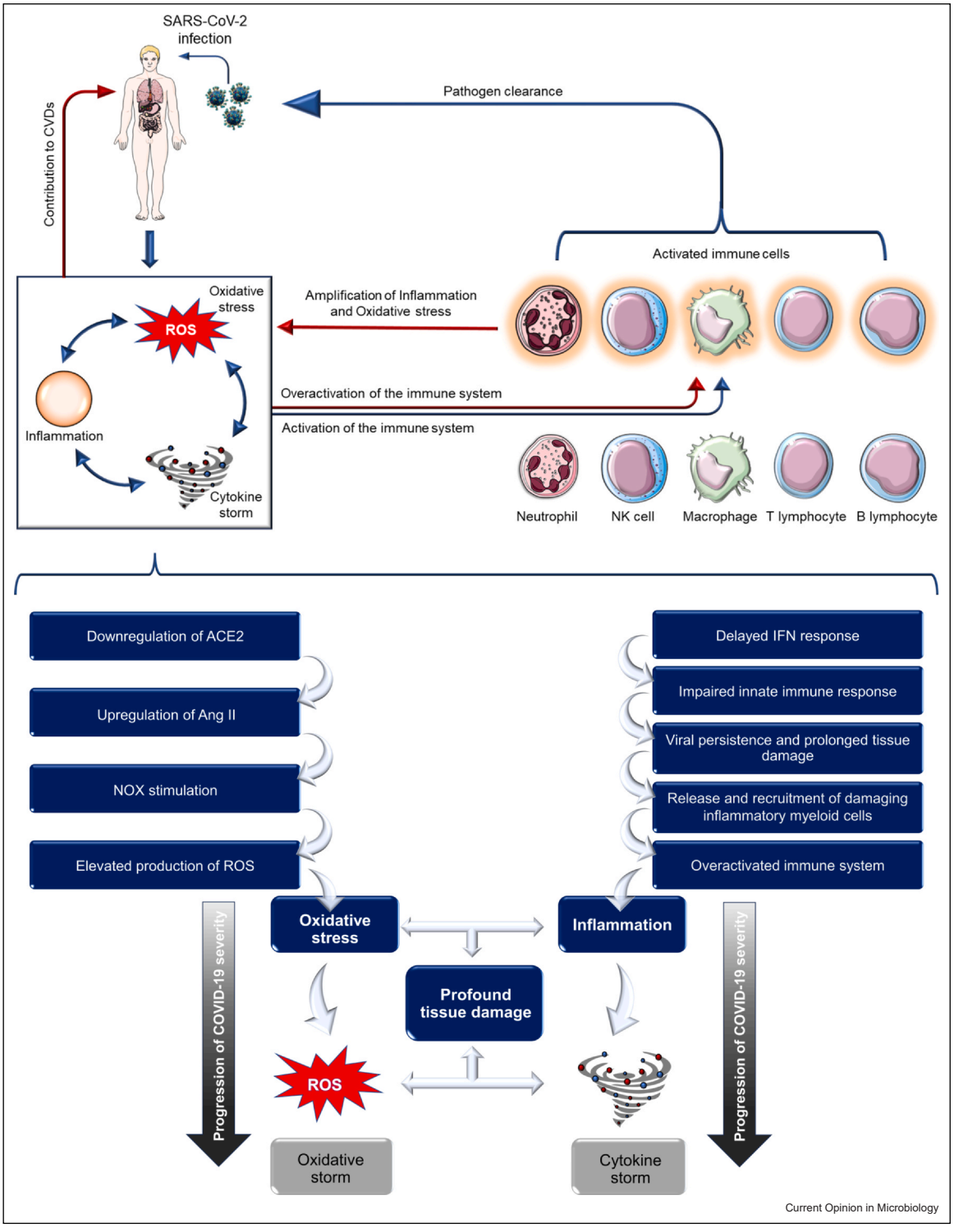
Structure and contractility of cardiomyocytes and its vasculature

Myocardial tissue injury has been observed in SARS-CoV-2-positive individuals, independent of pre-existing comorbidities [22]. Typical manifestations include disorganized myofibrils, an increase in cell size, and a reduction of the left ventricle ejection fraction, together indicating a hampering of contractile function [23]. In addition, cardiac arrhythmias and QT interval prolongation have been discovered in ICU patients. These were related to the elevation of cardiac biomarkers, viral spreading in the heart, and medication [24]. One group utilized phase-contrast X-ray tomography to scan SARS-CoV-2-infected, postmortem cardiac tissue and observed a rise in the prevalence of blood-filled capillaries, caused by the formation of microthrombi during infection. Furthermore, the group observed significant alterations in the vasculature, including changes in vessel size, branching, and intussusceptive angiogenesis, indicated by holes in the capillaries [25]. Even though cardiac injury might be a hallmark of SARS-CoV-2 infection, its manifestation was not elevated compared with other pulmonary infections, and no changes in mortality rates were observed [26].

Oxidative stress and cardiac mitochondria dysfunction

Oxidative stress, which occurs when reactive oxygen species (ROS) are excessively generated and the antioxidant system fails, plays a crucial role in causing cardiac damage during SARS-CoV-2 infection. One of the main triggers of ROS overproduction is the ACE2 downregulation after viral binding, which inhibits its proteolytic function. As a result, the concentration of angiotensin II increases, stimulating the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Figure 1). Moreover, IL-6 and TNF-α have the ability

Figure 1



The crosstalk between oxidative stress, inflammation, and CVDs in COVID-19 patients along with some key components such as ACE2, angiotensinogen II (Ang II), NOX, ROS, and IFN.

to enhance ROS production within mitochondria [27]. Conversely, increased mitochondrial ROS and lipid peroxidation activate the inflammasome, confirming that oxidative stress and inflammation can reinforce each other during SARS-CoV-2 infection [28]. Both oxidative stress and inflammation are typical indicators of cardiovascular diseases (CVDs), which increase the risk of adverse outcomes during infection [29]. Through molecular dynamics simulations, Fossum et al. found that pre-existing oxidative stress promotes SARS-CoV-2 binding to the ACE2 receptor by altering the viral structure and enhancing its affinity for the receptor [30]. Morphological and functional changes of cardiac mitochondria represent another typical manifestation of SARS-CoV-2-mediated cardiac damage and a major contributor to cell dysfunction, particularly boosted by oxidative stress via the NADPH oxidase (NOX) pathway (Figure 1) [31]. One study observed binding of viral proteins to mitochondrial proteins, presumably inhibiting the process of oxidative phosphorylation and, in turn, boosting glycolysis [32]. A recent experiment confirmed the potential of the S1 Spike protein to accelerate the accumulation of ROS, attenuate mitochondrial respiration, and increase mitochondrial fission and calcium levels, thereby leading to mitochondrial dysfunction in human cardiomyocytes (AC16). Interestingly, these effects were reversed upon blocking the ACE2 entry mechanism, providing evidence for SARS-CoV-2 exploitation of ACE2 for cellular infiltration [33]. These results were further elaborated by conducting RNA sequencing with SARS-CoV-2-infected human-induced pluripotent stem cell-derived cardiomyocytes. Alterations of gene expression were related to the complexes of the mitochondrial chain, the proinflammatory nuclear factor kappa B pathway, as well as heart contraction, all underscoring the potential to induce cardiomyocyte dysfunction with major contribution of mitochondrial failure [34]. Following the loss of mitochondria, it was observed that mitochondrial proteins accumulate in the plasma of severely infected patients, potentially initiating apoptosis, and local inflammation via cytochromes [35,36].

Taken together, the studies presented in this work provide a detailed explanation of how SARS-CoV-2 directly enters the heart and leads to damage, followed by invasion of immune cells in the pericardium. This process is accompanied by inflammatory signaling and structural changes. It is important to note that excessive inflammation and oxidative stress, which are triggered by either invasion of SARS-CoV-2 in the myocardium or pre-existing CVDs, play a significant role in causing cardiac damage. Ultimately, these factors contribute to higher mortality rates.

Patient stratification and risk assessment: the roles of age, gender, and comorbidities

Given the potential severity of an infection with SARS-CoV-2, it is crucial to classify patient cohorts based on common physiological features to gain a deeper understanding of the underlying mechanisms of cardiac damage and outcomes. Therefore, many studies aimed to identify high-risk patients.

Increasing age

One of the most striking and discussed risk factors for the susceptibility to more severe infection outcomes is increasing age. Older age significantly correlates with a higher in-hospital mortality rate [37,38]. Researchers also discovered a positive relationship between increasing age and marker levels indicating myocardial injury [39]. In alignment with this, an autopsy study, mainly consisting of elderly, unvaccinated individuals, observed myocardial infiltrates in four individuals, and one heart was diagnosed with acute myocarditis. Interestingly, among the 84 distinct anatomical locations and body fluids tested, the viral burden and inflammatory bursts outside the respiratory system were comparatively low [40].

Male gender

Increasing evidence has been collected regarding gender-based pathology during infection, noticing an elevation of adverse outcomes and complications in males [41]. The same observation was made in a US patient cohort, discovering an even more pronounced gender difference in older age [42]. Whether the dissimilar course of infection arises from hormonal influence, lifestyle, or different immune response in males and females is currently under investigation.

Comorbidities

Among hospitalized SARS-CoV-2 patients, hypertension, obesity, and type 2 diabetes represent the most frequent comorbidities [43,44]. Kamath et al. verified a positive correlation between patients characterized by hypertension, heart failure, cardiomyopathy, and ventilation risk. Accordingly, these patients exhibit higher mortality rates. Furthermore, acute myocarditis and elevated levels of troponin exacerbate clinical outcome and worsen prognosis in patients [45].

Diabetes mellitus and obesity are two, often intertwined, chronic disorders with rising prevalence worldwide. The nature of obesity, with elevated levels of glycerol, proinflammatory cytokines, and hormones, favors the development of insulin resistance and, consequently, the development of diabetes [46]. During the pandemic, epidemiological studies raised the awareness that diabetes and obesity highly contribute to an increase in morbidity and mortality rates following SARS-CoV-2 infection [47]. Further evidence was obtained from a murine model used by Johnson et al., in which diabetic/obese mice were more prone to attenuation of virus clearance and increased numbers of neutrophils inside their lungs [48].

Hypertension, diabetes mellitus, and obesity together are known risk factors for the development of acute

myocardial infarction (MI) [49]. An infection with SARS-CoV-2 has been shown to be especially fatal in MI patients. A total of 129 hospitalized MI patients simultaneously treated for SARS-CoV-2, were enrolled, and subsequently monitored. Compared with the control group (noninfected MI patients), in-hospital mortality was significantly elevated (1.6% vs 24%), with the worst outcome in the subgroup of patients requiring intensive care (4.3% vs 87%) [50].

Diagnostic and prognostic markers

Several biomarkers to confirm virus-associated myocardial damage have been recognized in clinical routine work. Elevated levels of natriuretic peptides and cardiac troponins are established diagnostic markers, and interestingly, it was confirmed that they can be independently assessed to predict in-hospital mortality [39]. More specifically, N-terminal pro-B-type natriuretic peptide (NT-pro BNP) was found to be a predictor of in-hospital mortality in patients with and without existing heart failure [51]. In compliance with these discoveries, another study further confirmed troponin-I ultra as a promising diagnostic marker for in-hospital mortality, alongside creatinine kinase–myocardial band [38].

Cardiac manifestations of long coronavirus disease

Recently, a rising number of publications have emerged, stressing out the pivotal role of ongoing cardiac pathophysiology in prolonging SARS-CoV-2 symptoms. Noteworthy, postacute COVID or long COVID manifestations were not exclusively observed in risk patients but also in mildly or asymptomatic infected individuals.

The large cohort study of Xie et al. investigated the incidence of cardiovascular complications related to long COVID, using over 153 000 individuals who were previously infected. The results show a higher 1-year burden for those who were exposed to the virus compared with noninfected individuals. Typical cardiac-related manifestations of long COVID included ischemic and nonischemic heart disease, arrhythmias, pericarditis, myocarditis, heart failure, and thromboembolic disease, even in nonhospitalized patients [52]. In concordance with these findings, a recent study from Germany observed ongoing cardiovascular involvement in former patients, independent of hospitalized or home recovery, as well as the severity of the infection. Over one-third of the enrolled patients complained about shortness of breath after an average period of 71 days after their positive test. High-sensitivity troponin T was still elevated in 71% of the patients, and typical findings included reduced ejection fractions in both chambers, a higher left ventricular volume, and elevated T1 and T2 measures, indicating ongoing inflammation of the myocardium [53].

Cardiac outcomes in individuals with mild or asymptomatic infection have been specifically investigated by Puntmann et al. From 346 enrolled individuals, 57% showed cardiac symptoms almost 1 year after infection, further suggesting persistent inflammatory responses in cardiac tissue. Interestingly, a higher prevalence could be observed in women [54]. Indeed, despite a higher chance of males to develop adverse infection outcomes, current literature has noted a significant increase in the incidence of long COVID in females on both physiological and psychological levels [55]. Regarding former severely infected patients, Fagyas et al. investigated the role of anticardiac autoantibodies, which were observed in two-thirds of their patient cohort. While the infection-free heart failure group showed a similar occurrence of IgG antibodies, the IgM autoantibodies were significantly elevated in the SARS-CoV-2 patients, potentially hampering recovery success and thus promoting long COVID [56]. Given the functionality of SARS-CoV-2 to suppress the host's immune response and the known feature to damage DNA, Mitrofanova et al. found a 1.5-fold increase in heart tumor incidence in patients post-COVID [57].

In summary, current literature suggests that cardiac manifestations of long COVID occur independently of disease severity. These manifestations can range from mild symptoms, such as elevated markers in the blood, to more serious cardiovascular complications, such as arrhythmias, heart failure, or ongoing inflammation.

Therapeutic implications for cardiac repair and prevention

The development of vaccines was the first and most prominent approach to lower the incidence of severe infection during the COVID-19 pandemic, also raising voices of concern, given the limited time for proper assessment of side effects before official approval. Two independent studies report cardiac side effects emerging from the use of mRNA vaccines, including Spikevax (Moderna) and Comirnaty (Pfizer/BioNTech), potentially leading to the development of myocarditis and pericarditis, especially in young males [58,59]. Nevertheless, both studies acknowledge the effectiveness of vaccine administration in lowering adverse infection outcomes, outweighing underrepresented side effects.

On a side note, the COVID-19 treatment landscape changed over time after a rising number of publications emerged, criticizing the commonly used remdesivir and hydroxychloroquine in the early stage of pandemic. Merches et al. utilized murine and human cell culture models and found significant alterations of cardiomyocyte contractility, mitochondrial, and kidney injury using remdesivir concentrations similar to official recommendations [60]. In the case of hydroxychloroquine,

several studies independently discovered no beneficial effects to alleviate COVID-19 symptoms; on the contrary, multiple side effects might arise, dominantly seen in older patients and those with comorbidity burden [61]. Nowadays, the oral antiviral drug Paxlovid has been widely approved for the clinical treatment of SARS-CoV-2 patients and exhibits significant reductions in mortality rate in patients with pre-existing heart complications. It inhibits the replication of SARS-CoV-2-RNA and has been proven effective against all current virus variants. However, the use of Paxlovid should be closely monitored and evaluated due to potential negative effects on redox homeostasis and endoplasmic reticulum function [62]. In a specific group of patients with acute myocarditis, the IL-6 receptor antagonist Tocilizumab was prescribed, and it improved infection outcomes and cardiac function and reduced cardiac biomarkers, leading to significantly higher survival rates compared with the COVID myocarditis group that received different medication (80% vs 24%). This improvement was demonstrated by lower levels of miR-21 and TnI, as well as increased ejection fraction. However, the patients were not followed up after discharge from the hospital, which is a limitation of this study [63]. In the course of myocarditis, it was proposed to further subclassify the patients, as researchers and clinicians have identified two distinct phenotypes: the classical MIS-A$^-$ (multisystem inflammatory syndrome in adults) myocarditis occurring in early phases of infection and the MIS-A$^+$ type representing a rare complication after infection, typically affecting young, male individuals [64]. For the subgroup of diabetic patients, metformin proved effective. Previous studies from China, France, and the United States observed significant alleviations of SARS-CoV-2–associated mortality in patients who were treated with metformin before infection. Currently, metformin administration has been identified as an independent predictor of survival in both males and females. However, further studies should focus on classifying patients with diabetes types I and II. It is still unclear whether metformin could be effective for infected, nondiabetic patients [65]. Another potential therapy is the hypotensive drug captopril, which was recently evaluated by Huang et al. due to its ability to inhibit ACE. Their initial findings confirmed that the drug affects the TNF signaling pathway, resulting in reduced inflammation and apoptosis in cardiomyocytes, as well as a slight recovery of ACE2 expression *in vitro*. Nevertheless, its effectiveness *in vivo* during SARS-CoV-2 infection requires further investigation [66]. However, infection recovery and health maintenance depend on multiple factors apart from clinical care. Lifestyle changes have proven to be efficient in decreasing the incidence of long COVID symptoms. An important mediator of recovery and future infection prevention is weight loss. A new study from Japan with over 2 million participants investigated the correlation of increased body mass index with the risk of SARS-CoV-2 infection. Interestingly, the group concluded that a weight loss significantly lowered the infection risk and severity [67]. Noteworthy, individuals who stayed physically active before and during the pandemic exhibited a significantly lower risk for the incidence of long COVID [68].

It is also worth mentioning that novel technologies are under development. In the work of Aguida et al., the authors describe the utilization of near-infrared light exposure. Mitochondrial metabolism was stimulated to produce antioxidants, leading to an alleviation of proinflammatory signals caused by the SARS-CoV-2 infection. In a clinical setup, patients receive light doses (730 nm wavelength) that can penetrate the skin [69]. For future patient handling, it would be conceivable to combine this approach with the administration of drugs.

Conclusions

An infection with SARS-CoV-2 has the potential to manifest a diverse set of cardiovascular health problems, including myocardial tissue damage, arrhythmia, myocarditis, and pericarditis. The main underlying pathophysiological mechanisms of morbidity and mortality are ongoing inflammation, with TNF-α and ILs as key mediators, oxidative stress, altered immune response, and subsequent apoptosis within cardiac tissue, alongside genomic changes. Evaluation of existing comorbidities showed an increased chance of adverse infection outcomes in elderly, male, unvaccinated individuals, and such characterized by pre-existing cardiovascular complications, diabetes, and obesity. Taken together, evidence is pointing toward prolonged COVID symptoms with cardiac involvement in some individuals, independent of infection severity, making it difficult to ascertain risk factors and biomarkers able to predict long COVID. Upon now, the exact mechanisms are not entirely understood, and investigations should be expanded before more profound conclusions can be drawn, also considering the higher long COVID prevalence in females. The risk for prolonged cardiac manifestations of COVID-19 can be alleviated by lifestyle changes, including healthy diets, weight loss, and sports, as well as clinical monitoring for diagnostic markers. In light of the wide range of potential comorbidities and risk factors, it is crucial to closely monitor the potential side effects of drug treatment options. Despite the ongoing debate, the studies presented provide strong evidence for the effective reduction of hospitalization and mortality rates, globally ensuring the recovery of high-risk patients. Successful treatment can be achieved by targeting viral replication, as well as the persistent inflammatory and oxidative state within the heart.

Nevertheless, it is important to acknowledge several limitations in the scope of this topic. One limitation of

the studies presented is the absence of cardiovascular parameters in mildly infected and asymptomatic individuals during the acute phase of infection. This is often due to limited biopsy availability and size [12]. Additionally, it is crucial to note that the cardiac manifestations and in-hospital mortality rates cannot be broadly applied due to two factors: (1) ethnic disparities [70] and (2) the presence of pandemic waves with different dominant variants of SARS-CoV-2, resulting in changes in the clinical landscape [3].

CRediT authorship contribution statement

M.T.: Conceptualization, Visualization, Writing – original draft. **M.J.:** Conceptualization, Visualization, Writing – original draft. **I.A.:** Writing – review & editing. **I.E.L.-B.:** Writing – review & editing, Funding acquisition. **N.H.:** Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-assisted technologies in the writing process

Generative AI and AI-assisted technologies have not been used.

Data Availability

No data were used for the research described in the article.

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- •• of outstanding interest

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